REMARKS

Claims 1-4 and 6-28 are pending. Claims 1-4, 6-10 and 15-25 are active. Like the elected claims, Claim 14 is also directed to a method of detecting, and not to a product, therefore, the Applicants respectfully submit that this claim should be rejoined to the elected group of claims.. To help further clarify the invention, the Applicants attach herewith a Declaration further describing and elaborating on the advantages of the invention. Also, as suggested by the Examiner, Claims 1-4, 9, and 14-17 have been amended to recite a final detecting step that relates back to the preambles of these claims. Support is found in the original claim language and on pages 2-7 of the specification. Support for new Claim 24 is found in original Claim 5. New Claims 25-28 depend from Claim 24 and find support in original Claim 5 and Claims 6-9. Accordingly, the Applicants do not believe that any new matter has been added.

RESTRICTION

Applicants hereby affirm their prior election with traverse of Group I, Claims 1-10 and 15-20 and respectfully request that Claim 14 be rejoined to the elected claims. Claim 14 is directed to a method of detecting, and not to a polynucleotide, and should therefore be grouped with Claims 1-10 and 15-20. Rejoinder is therefore respectfully requested.

REJECTION--35 U.S.C. 112, SECOND PARAGRAPH

Claims 1-10 and 15-20 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The bodies of Claims 1-4, 10 and 15-17 have been amended to relate back to the preamble and Claim 20 has been amended to delete the phrase "capable of". Accordingly, these rejections may now be withdrawn.

REJECTION--35 U.S.C. 102(e)

Claims 1-4 were rejected under 35 U.S.C. 102(e) as being anticipated by Lonial et al., U.S. Patent 6,001,560. Lonial does not anticipate the present invention, because it is directed to a simple promoter gene assay for determining whether a compound exerts IFN-γ activity, and not to a method for determining whether a test substance disrupts the activity of an endocrine hormone present in the medium in which a cell is cultured. Moreover, the promoter gene assay of Lonial does not detect an endocrine disrupting action of a test substance by comparing the gene expression patterns of cells exposed to the test substance in the presence of the endocrine hormone, and those not exposed to it.

On the other hand, the present invention detects the endocrine disruption activity of a test substance based on a differential display method. This method measures differences in gene expression in the presence of, and absence of, a particular test substance, e.g., an endocrine hormone disrupting substance, such as dioxin. The effect of the test substance is determined by comparing the expression patterns of the cells exposed to the test substance, with the expression patterns of cells not exposed to the test substance. By culturing the cells in the presence of the endocrine hormone, the disruptive effects of the putative test substance can be accurately determined under more natural conditions, e.g., in the presence of the natural endocrine hormone to which hormonally-sensitive cells in an animal would normally be exposed. The advantages and distinguishing features of the present invention are further described in the attached Declaration.

On the other hand, Lonial is directed to a promoter gene assay method for determining whether a substance exhibits an IFN-γ like activity based on expression of a reporter gene (e.g. a growth hormone gene) that has been constructed and transformed into a

reporter cell line. Such a method uses a specific cell for observing a specific action (i.e. IFN-γ action) and does not detect an unspecified action such as an endocrine disrupting action. Lonial does not describe the method of the present invention that comprises detecting an endocrine disrupting action of a test substance by (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and test substance and (2) comparing the gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance.

Lonial does not disclose culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and a test substance, or disclose comparing the gene expression patterns of cells exposed to the test substance, with those not exposed to the test substance. For instance, Claim 12 of Lonial is directed to contacting a transformed cell line with a sample suspected to containing a human IFN-γ agonist and measuring the level of expression of a reporter gene (e.g., growth hormone). Lonial do not disclose (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and a test substance, and (2) comparing the gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance.

Unlike the present invention, Lonial is not concerned with whether a substance (e.g., dioxin) exhibits an endocrine hormone disrupting action, only with whether a particular compound exhibits an IFN-γ like activity as measured by the expression of a reporter gene, such as a growth hormone gene that has been transformed into a cell line. Moreover, the method of Lonial would be ineffective, if the cell lines which express growth hormone reporter gene were grown in the presence of growth hormone, as the level of secreted growth hormone protein from the reporter gene could not be accurately measured.

Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

REJECTION--35 U.S.C. 103

Claims 1-4, 7, 9 and 15-17 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lonial et al., U.S. Patent 6,001,560, in view of Gilles et al., U.S. Patent 4,663,281. Lonial and Gilles do not render the invention obvious, as neither document suggests a method for detecting an endocrine disrupting action of a test substance by (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and test substance and (2) comparing the gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance.

As discussed above, Lonial is directed to determining whether a substance exhibits an IFN-γ like activity based on expression of a reporter gene (e.g. a growth hormone gene) and is not concerned with whether a substance (e.g., dioxin) exhibits an endocrine disrupting action.

Gilles is directed to a method for enhancing the production of proteins in eukaryotic cells and does not describe a method for testing whether a substance (e.g., dioxin) exhibits an endocrine disrupting action. Fig. 2 of Gilles shows an autoradiogram of radiolabelled proteins produced by cell lines transfected with different plasmids; Fig. 7 shows a Southern blot comparing the DNA's of cells transfected with different plasmids; and Fig. 8 shows a Northern blot comparing the RNA's of cells transfected with different plasmids. However, none of these assays were performed by (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and putative endocrine disrupting test

substance and (2) comparing the gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance.

Moreover, none of the cited prior art suggests the advantages of the present invention which are shown in the attached Declaration. As shown in Table 3 of the Declaration, the present invention makes it possible to detect the difference in the expression numerous different genes associated with an endocrine disrupting action, when such gene expression was not be detected by a comparable conventional method (e.g., a method that did not culture cells in the presence of an endocrine hormone). Graph 1 of the Declaration shows the effects of dioxin on five different types of genes specifically identified by the method of the present invention in the presence of the endocrine hormone T3. However, conventional methods that did not culture cells in the presence of the T3 hormone, did not identify the ability of dioxin to disrupt these genes or identify the sensitivity of these genes to dioxin.

Accordingly, as the prior art does not disclose or suggest the invention, or the superior ability of the invention for identifying particular endocrine disrupting compounds or genes responsive to such disruption, the Applicants respectfully request that this rejection be withdrawn.

REJECTION--35 U.S.C. 103

Claims 1-4, 8 and 10 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lonial et al., U.S. Patent 6,001,560, in view of Pearson et al, U.S. Patent 5,916,779. Lonial and Pearson do not render the invention obvious, as neither document suggests a method for detecting an endocrine disrupting action of a test substance by (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and test substance and (2) comparing the gene expression patterns of cells exposed to the test substance and the cells

not exposed to the test substance. Lonial has been discussed above. Pearson is cited for its teachings of RT PCR on RNA recovered from a cell, however, it does not remedy the deficiencies of Lonial, because it does not suggest detecting endocrine disrupting substances by a differential display method in the presence of an endocrine hormone. Moreover, the cited prior art does not suggest the superior sensitivity of the present invention for identifying particular endocrine disrupting compounds or genes responsive to such disruption. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

REJECTION--35 U.S.C. 103

Claims 1-6 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lonial et al., U.S. Patent 6,001,560, in view of Comoglio et al., U.S. Patent 6,030,949, further in view of Cubicciotti, U.S. Patent 6,287,765 B1. Lonial, in view of Comoglio and Cubicciotti do not render the invention obvious, as these documents do not suggest a method for detecting an endocrine disrupting action of a test substance by (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and test substance and (2) comparing the gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance. Comoglio, Examples 2 and 3, is cited for its teaching of Neuro2a cells and Cubicciotti for its teaching of the hormone triiodothyronine. However, neither of these documents discloses the method of the present invention involving (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and test substance and (2) comparing the differential gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance. Thus, these documents do not remedy the deficiencies in Lonial. Moreover, the cited prior art does not suggest the superior ability of the present invention for identifying particular endocrine

disrupting compounds or genes responsive to such disruption. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

REJECTION--35 U.S.C. 103

Claims 1-6 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lonial et al., U.S. Patent 6,001,560, in view of Gilles et al., U.S. Patent 4,663,281, further in view of Comoglio et al., U.S. Patent 6,030,949, further in view of Cubicciotti, U.S. Patent 6,287,765 B1. As discussed above, none of the cited documents disclose or suggest a method of (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and test substance and (2) comparing the differential gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance. Moreover, the cited prior art does not suggest the superior ability of the present invention for identifying particular endocrine disrupting compounds or genes responsive to such disruption. Accordingly, this rejection may now also be withdrawn.

REJECTION--35 U.S.C. 103

Claims 1-6 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lonial et al., U.S. Patent 6,001,560, in view of Gilles et al., U.S. Patent 4,663,281 further in view of Makari, U.S. Patent 4,752,471. As discussed above, Lonial and Gilles do not disclose or suggest a method of (1) culturing a cell sensitive to an endocrine hormone in the presence of the endocrine hormone and test substance and (2) comparing the gene expression patterns of cells exposed to the test substance and the cells not exposed to the test substance. Makari, Claim 5, is cited for its teaching of recovering a glycoprotein by cutting off the polysaccharide chain. However, Makari does not remedy the primary deficiencies of Lonial or Gilles, as discussed above. Moreover, the cited prior art does not suggest the superior

sensitivity of the present invention for identifying particular endocrine disrupting compounds or genes responsive to such disruption. Accordingly, this rejection may now also be withdrawn.

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

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